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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,854	03/21/2002	Andrew Austen Mortlock	Z70601-1	6749

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EXAMINER	
TRUONG, TAMTHOM NGO	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 03/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,854	MORTLOCK ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12-27-04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *7-10,13 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,11,15 and 16* is/are rejected.

7)☒ Claim(s) *5, 6 and 12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3-21-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

It is acknowleged that applicants have elected group 2 with traverse (claims 1-6, 11, 12, 15 and 16 (part of each – wherein R^5 is $-Z-(CH_2)_nR^9$ and R^1-R^4 is hydrogen or alkyl; or compounds of formulae II and IIB). The traversal is on the following grounds:

- There is "*no undue burden in examining all of the claimed subject matter*".
- Applicants asserted that all claims were searched simultaneously in the International Search Report, and therefore, "*it is not credible that search and examination of the entire claim set presents an unreasonable burden.*"
- Applicants also cited MPEP 803 which stated that if there was no burden of searching and examination, then the entire application must be examined even though there were claims to independent and distinct invention.
- Applicants requested that the inventions of groups 1 and 3-7 be combined with the claims of group 2.

The above traversal and request are not found persuasive for the following reasons:

A CAS search for the compounds of group 2 alone yields a total of 3137 hits in the Registry File, and 107 hits in the CAPLUS file. Note, the lower number of hits in the CAPLUS file is due to combining the structure with various intended activities. Without such a combination, there would have been a larger number of hits.

Note also, a search in EAST yields 674 hits. Therefore, the total number of hits from both data bases is 781. That is a fairly large volume of references.

Quinazoline compounds with substituents as set forth in the claims are abundant in the

art. With the extensive list of substituents represented by $-X^1R^{14}$, it is very difficult to formulate a search that would yield prior arts that are relevant and specific. In the instant case, the undue burden of searching and examining comes from formulating a search that is broad enough for formula I, which must also covers the scope of formula II or IIB.

The International Search Report provides a preliminary search, but not necessarily a complete search. Such a report cannot be relied on as a search of the entire claim set. Therefore, said report does not relieve the examiner from the burden of searching and examining. Besides, "burden of searching" is not the criterion for making "lack of unity". The main criterion for "lack of unity" is a common special technical feature. In the instant case, all though the groups share the *quinazolinyl* ring, such a ring does not define the invention, and is not a contribution to the art. Thus, the *quinazolinyl* ring alone is not a common special technical feature, and so, the "lack of unity" is justified.

Under 35 U.S.C. 372(b)(2), "*international applications designating but not originating in, the United States...the Commissioner may cause the question of unity of invention to be reexamined under section 121 of this title...*" Thus, as discussed above, the instant invention clearly lacks unity according to PCT 13.2. Accordingly, restriction under 35 U.S.C. 121 and 372 is deemed necessary.

Regretfully, applicants' request for combining groups 1, and 3-7 with group 2 cannot be accommodated.

The restriction requirement is still deemed proper and is therefore made FINAL.

Claims 7-10, 13 and 14 are withdrawn from consideration as being drawn to the non-elected subject matter.

Claim Objections

1. Claims 5, 6 and 12 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must refer to preceding claims in the alternative language. See MPEP § 608.01(n). Accordingly, the claims 5, 6 and 12 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-4, 11, 15 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. Claim 1 recites the limitation of a "*method for inhibiting aurora 2 kinase*" which has indefinite metes and bounds because it is unclear what diseases are treated. Although the inhibition of a kinase typically treats cancer, it is unclear what other diseases can also be treated.

b. Claim 1 recites the limitation of "*optionally substituted hydrocarbyl group*" (e.g., definitions of R^5 and R^9) which has indefinite metes and bounds because a substituted *hydrocarbyl group* include an infinite number of combinations of a hydrocarbyl group with an unlimited number of functional groups and/or rings. Thus, it is unclear as to the structure of a "*substituted hydrocarbyl group*" in terms of the number of atoms, functional groups, and/or rings as well as the connection between said atoms, functional groups and/or rings with the hydrocarbyl group.

c. Claims 1 and 11 recite the phrase *"(other than ethenyl substituted by a carboxy group or an amide or sulphonamide derivative thereof)*". It is unclear if said phrase is a proviso, or if said phrase is meant to define the "*substituted hydrocarbyl group*" as being **more** than a substituted ethenyl group.

d. Claims 1, 11, 15 and 16 recite the limitation of "*ester, amide or prodrug thereof*" which renders said claims indefinite because "*ester, amide*" are narrow limitations while "*prodrug*" is a broad limitation, and it is unclear which set of limitation is intended.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature

introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

e. Claims 1-4, 11 and 16 recites limitations within parentheses (e.g. "(wherein...)" or "(linked via...)", etc.) which are unclear if said limitations are part of the claims, or they merely serve as examples.

f. The proviso in claim 16 makes the definition of R^{67} unclear since by the proviso, the alkoxy group represented by R^{67} must always be substituted, and not optionally substituted as stated at the beginning of the definition for R^{67}. Clarification is solicited.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Scope of Enablement:** Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of colorectal cancer, does not reasonably provide enablement for the treatment of other diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claim 1 recites a "*method for inhibiting aurora 2 kinase in a warm blooded animal in need of such treatment...*" which covers the treatment of an array of diseases including those that have yet to be discovered. Claims 2-4 depend on claim 1, but they recite subgenera of formula (I).

The amount of direction or guidance presented: The specification only provides *in-vitro* assay for aurora 2 kinase inhibition, and no *in-vivo* assay to show if the claimed compounds can reduce tumor size, or treat any disease. The mechanism of inhibiting cell growth is generally known for treating cancers and tumors. However, such a mechanism is also known for its high risk in decreasing the production of blood cells as well as other cells' growth that is necessary for maintaining patient quality of life. Without a guidance for a safe and effective use of the claimed compounds, the skilled clinician would have to carry out undue experimentation to establish an

efficacy and safety profile for each of the claimed compound in the treatment of each related disease.

The state of the prior art: Currently, the inhibition of aurora 2 kinase is related to the treatment of colorectal cancer as evident by the study of **Bischoff et. al.** Therefore, following such a finding, the skilled clinician would be able to use the claimed compounds in the treatment of colorectal cancer only.

The relative skill of those in the art: Even with the advanced training, the skilled clinician would have to engage in undue experimentation to establish data that would adequately support the use of the claimed compounds in the treatment of diseases other than colorectal cancer. Such a task would require a tremendous amount of effort, time and resources.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the specification only shows *in-vitro* data for the inhibition of aurora 2 kinase, which do not adequately guide the skilled clinician in the treatment of diseases other than colorectal cancer. Thus, with such a limited teaching, the skilled clinician would have to carry out undue experimentation to use the claimed compounds in the method that is unduly broad as recited in claims 1-6.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 11, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Thomas et. al.** (US 6,184,225 B1 or 6,291,455 B1). On column 41 of US'225, Example 17 discloses a compound of *4-(4-chloro-2-fluoro-5-hydroxyaniline)-6-methoxy-7-(3-morpholinopropoxy)quinazoline* which is analogous to a compound of formula IIB with the following substituents:

i. X is NH;

ii. R^1 and R^4 are hydrogen (or $-X^1R^{14}$ wherein X^1 is a direct bond, and R^{14} is hydrogen);

iii. R^{66} is an optionally substituted alkoxy or $-X^1R^{14}$ wherein X^1 is O, and R^{14} is hydrocarbyl);

iv. R^{67} is morpholinopropoxy;

v. Z is O; n = 0; R^9 is hydrogen; or $-Z-R^9$ is a hydroxy group;

vi. R^6 and R^7 are halogens.

The compound differs from the claimed formula IIB by having the hydroxy group (corresponding to the instant $-Z-R^9$) at the 5th position, and not at the 4th position on the phenyl ring (as in formula IIB). However, the disclosed generic formula I on column 2 (US'225) allows the substituents (R^3) to be anywhere on the phenyl ring, and thus, provides the equivalent teaching for substituents at all positions on the phenyl ring. That is, the generic teaching of US'225 provides the equivalent teaching for all positional isomers (i.e., ***ortho-*** *(2nd & 6th positions),* ***meta-*** *(3rd & 5th positions), and* ***para-*** *(4th position))* of the substituted phenyl ring. Therefore, one of the ordinary skill in the art would have been motivated to make a positional

isomer of the disclosed compound with the hydroxy group at the 4th position on the phenyl ring because such an isomer would have been expected to have the same VEGF inhibitory activity, and treat cancer as well.

The general process for making the disclosed quinazoline compound (recited in the instant claim 12) is taught on column 19. Note, the disclosed intermediate, formula XIX is corresponding to the instant formula VII. The disclosed intermediate, formula XX is corresponding to the instant formula VIII.

The pharmaceutical composition (recited in the instant claim 15) is also taught on column 24 of US'225.

Thus, at the time of the invention, it would have been obvious to make and use a positional isomer as recited in claims 11, 15 and 16 in view of Thomas et. al.

No pending claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (10:00-6:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Tamthom N. Truong
Examiner
Art Unit 1624

2-28-05

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